REMARKS

Claim 12 has been amended to include the phrase "wherein said treatment results in a reduction in tumor size or a reduction in the level of a tumor marker." New claim 23 has been added. Support for new claim 23 can be found at page eight of the specification and in example 1. Claims 12-23 are pending. The specification is amended to change the title of the application to "Uses of Et 743 for Treating Cancer."

Obviousness-type Double Patenting

Claims 12-22 are provisionally rejected as unpatentable over claims 1-19 of co-pending application 10/492,320. Since the rejection is provisional and US 10/492,320 is awaiting examination, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, and apply any double-patenting rejections deemed necessary by the Examiner to the later application, as directed by the MPEP:

> If the "provisional" double patenting rejection is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent. (MPEP 804.1B)

35 U.S.C. § 103(a)

Claims 12-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Taama et al., *Eur. J. Cancer*, in view of Barrera et al., *Prodeedings of the American Association for Cancer Research*, Izbicka et al, *Annals of Oncology* and *Drugs Fut* (1997). Applicants respectfully traverse this rejection.

As amended herein, claim 12 now contains the limitation "wherein said treatment results in a reduction in tumor size or a reduction in the level of a tumor marker." Support for this amendment is found in the table of Fig. 1 and in examples 1-3. The Figure and examples describe the response of cancer patients who have been treated with ET 743 using the terms complete response (CR), partial response (PR), time to progression, stable disease and reduction in the levels of tumor markers such as CA-125. These are well defined terms of art in the cancer treatment field (see Therasse et al., *J. National Cancer Inst.*, 92(3):205-16, 2000; Green et al., *Investigational New Drugs*, 10:239-253, 1992; Miller et al., *Cancer*, 47:207-214, 1981). Complete response means that the tumor is no longer detectable. Partial response means that there has been a 50% reduction in tumor size. Time to progression is defined as the time from a clinical response, such as a complete or partial response to the time when the tumor reappears. Stable disease means that the tumor has stopped growing and has not spread. Levels of certain tumor markers such as CA-125 and CA 15-3 are known to correlate with status of some tumors (Rustin et al., *Clinical Cancer Research*, 10:3919-3926, 2004). A reduction in the level or the elimination of the tumor marker serves as an indication of a reduction in tumor size or growth. As discussed in more detail below, the disclosures in Fig. 1 and examples 1-3 provide ample evidence that treatment of human cancer patients with ET743 can result in a reduction in tumor size and/or a reduction in levels of tumor markers.

For the eleven patients whose clinical results are described in table 1, two had a complete response, 4 had a partial response and 4 had a minimal response. One of the complete responses lasted 29 months without signs of recurrence while 2 of the partial responses were continuing for 10 and 15 months without signs of recurrence. In example 1, 36 patients with soft tissue sarcoma or gastrointestinal stromal tumor were treated and 10 of the patients had stable

disease or minor response. In example 2, 20 advanced breast cancer patients were treated and 2 partial responses and 6 disease stabilizations were observed. In addition, 2 patients had a sustained decrease in the breast tumor marker CA 15-3. In example 3, 39 patients with sarcomas were treated. Four of the patients had a partial response, 3 had a minor response and 11 had their disease stabilized, most for at least 3 months. Two of the patients with a partial response had a complete response after surgery.

It is also important to point out that most of the patients described in table 1 and examples 1-3 had received at least one prior course of treatment with another anti-tumor agent that was unsuccessful. It certainly cannot have been predicted that any of these patients would respond to another anti-tumor agent, yet as described above, a number of them did respond to ET 743 and in some cases had complete responses.

In contrast, none of the four references cited by the Examiner teach or suggest, either alone or in combination, a clinical response in a human patient treated with Et 743. Taamma et al. describes the treatment of patients with ET 743 in a phase 1 clinical trial but provides no evidence that a clinical response has been seen in any of the patients. To the contrary, the statement is made that "Dose-escalation continues, currently nearing the expected pharmacoactive range level." This statement indicates that a dose that would be expected to produce a clinical response had not even been reached yet.

Barrea et al. describes *in vitro* treatment of human tumor cell lines with ET 743 in combination with several cytotoxic anti-tumor agents. There is no disclosure of treatment of human patients and certainly no disclosure of an efficacious clinical response to treatment with ET 743.

In a similar manner, Izbicka et al. describes an *in vitro* soft agar cloning assay used to evaluate the effect of ET 743 on primary human tumor specimens. There is no disclosure of treating human patients with ET 743. The disclosure in *Drug Fut*, vol. 22, no. 11 page 1279, 1997, describes the activity of ET 743 in *in vitro* studies using tumor cell lines and in *in vivo* studies in nude mice bearing human tumor xenografts. Beyond acknowledging that ET 743 is in phase 1 clinical trials, there is no disclosure in this reference of treating human patients with ET 743 and no evidence of an efficacious clinical response in human patients is presented.

The Applicants assert that the references cited by the Examiner, alone or in combination, do not teach or suggest all of the limitations of independent claim 12 as amended herein and therefore do not constitute a *prima facie* case of obviousness for claim 12 or the claims dependent from it. In particular, the cited references do not teach or suggest a reduction in tumor size or a reduction in the level of a tumor marker. Therefore the applicants respectfully request withdrawal of the rejection.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 13-4500, Order No. 4126-4007.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 4126-4007. A DUPLICATE OF THIS SHEET IS ATTACHED.

Respectfully submitted,
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Dated: March 23, 2006

By: _____
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